We report a rare presentation of an unusual disease—mucormycosis. Pulmonary infection is well known for its acute onset and rapidly fatal outcome. However, we encountered a case with an unusual presentation; our patient had a posttraumatic osteolytic rib lesion, localized pneumonitis, an exudative pleural effusion, and a subsequently metastatic abdominal wall abscess.

The site of primary infection or the portal of entry in our case is debatable. The patient probably inoculated her skin and soft tissue with environmental Rhizopus spores after she fell, and osteomyelitis of the adjacent rib and the pleural effusion developed as a consequence. Another possible route of infection, although one that is less likely, is through inhalation of the Rhizopus spores into the lower respiratory tract; such inhalation could have led to localized pneumonitis, pleuritis, and, eventually, osteomyelitis of the rib. Our conclusion regarding the route of infection in this case is mainly based on the historical information provided by the patient. We attribute her risk of fungal infection to diabetes mellitus, chronic metabolic acidosis, immunosuppression, and chronic renal graft rejection. She was not undergoing dialysis, she had not received injectable iron, and an Elastoplast (Beribbersdorfs, Norwalk, CT) had not been used [9].

The diagnosis of visceral mucormycosis is often difficult. The results of blood cultures, fluid cultures, and immunologic studies are rarely helpful. In the present case, the results of all pleural fluid cultures were negative. Mucoraceae do not appear to be viable when tissue is ground or minced before culture, and the rate of recovery of these organisms is low even when optimal techniques are used [2]. Furthermore, the growth of the organism is significant only in cases where the disease is histologically proven because the organism is often a laboratory contaminant [10]. Histologic examination of necrotic tissue debris, scrapings, or purulent aspirates remains the gold standard for diagnosis of visceral mucormycosis. All necrotic specimens from immunocompromised hosts should be prepared with potassium hydroxide, and all these specimens should be stained and cultured so that fungi can be detected.

Chad Wanishsawad, Robert C. Kimbrough, Sallaya Chintratanalab, and Kenneth Nugent
Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas

References

Effect of Clarithromycin on the Pharmacokinetics of 2',3'-Didoxyinosine in Patients Who Are Seropositive for Human Immunodeficiency Virus

Clarithromycin is frequently prescribed for treatment of mycobacterial infections in patients infected with HIV [1]. However, clarithromycin inhibits hepatic cytochrome P450 enzymes responsible for the metabolism of drugs such as theophylline, terfenadine, and possibly rifabutin [2]. The antiretroviral agent 2',3'-didoxiyo-
nosine (didanosine or ddl) is used to treat persons infected with HIV [3–6] and is cleared through a combination of hepatic and renal mechanisms [7–9]. The toxic effects of ddl include peripheral neuropathy and pancreatitis, both of which occur more fre-
quenty at higher doses [4, 5]. Although the pathways of the metabolism of ddl have not been fully elucidated, clarithromycin has the potential to inhibit the hepatic metabolism of ddl. Since higher serum levels of ddl may lead to an increased incidence of toxic effects or intolerance to ddl, the present study was conducted to evaluate the effect of multiple oral doses of clarithromycin on the pharmacokinetics of ddl.

We recruited 12 HIV-infected adults (aged 27–64 years) who had been receiving a constant dosage of commercially available ddl (taken twice daily for at least 1 month). Eight of the subjects were classified as having AIDS on the basis of a history of opportunistic infection or a CD4 T helper cell count below 200/mm³. Each subject participated in the study for 8 days. Blood samples for pharmacokinetic analysis of ddl were collected on days 1 ("pretreatment") and 8 ("posttreatment") in the Clinical Research Center at the Medical College of Virginia hospitals. The subjects were instructed to take ddl on an empty stomach (1 hour before meals or 2 hours after) each morning (8:00 A.M.) and night (8:00 P.M.) at their previously prescribed dosage (range, 3.1–7.8 mg/kg·dl) throughout the study.

On the first day of the study, subjects were admitted to the Clinical Research Center and took their usual morning dosage of
Table 1. Pharmacokinetic parameters of ddl before and after treatment with clarithromycin.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>ddl alone</th>
<th>ddl + clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-12}$ (ng·h/mL)</td>
<td>1,300 ± 658</td>
<td>1,477 ± 504</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>912 ± 452</td>
<td>1,113 ± 437</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (min)</td>
<td>0.63 ± 0.38</td>
<td>0.67 ± 0.44</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.4 ± 0.22</td>
<td>1.5 ± 0.39</td>
</tr>
</tbody>
</table>

NOTE: No comparisons are statistically significant ($P > .01$ for all comparisons). All numbers are given as mean ± SD.

ddl with 8 oz of water after fasting for at least 7 hours. They continued fasting for 4 hours after receiving the dosage of ddl. During study days 2–7, the subjects continued to take ddl in their usual outpatient setting and took oral clarithromycin (Abbott Laboratories, Abbott Park, IL, lot no. 63-047-AA-21) according to the following schedule: 1,000 mg each morning and evening (along with ddl) for 7 additional days. On study day 8, the subjects again fasted for at least 8 hours before and 4 hours after taking their usual morning dosage of ddl, which was taken simultaneously with the last dosage of clarithromycin after readmission to the Clinical Research Center.

On study days 1 and 8, blood samples for analysis of ddl concentrations were obtained through an indwelling catheter at the following times (hours) after the dose of ddl was taken: 0, 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2, 3, 4, 6, 8, 10, and 12. Concentrations of ddl were determined by a validated RIA from commercially available reagents (Sigma Chemical Company, St. Louis, MO). Minimum ($C_{\text{min}}$) and maximum ($C_{\text{max}}$) serum concentrations of ddl, and time at which $C_{\text{max}}$ occurred ($T_{\text{max}}$), were determined by visual inspection of the data. The parameter of primary interest, the area under the concentration vs. time curve over 12 hours ($\text{AUC}_{0-12}$), was calculated by the trapezoidal rule. Differences in the pharmacokinetic parameters of ddl ($\text{AUC}_{0-12}$, $C_{\text{max}}$, $T_{\text{max}}$, and $t_{1/2}$) before and after treatment with clarithromycin were assessed with use of Wilcoxon’s signed rank test for paired comparisons. Because of multiple comparisons, Bonferroni correction was applied and a significant difference is defined as $P < .01$.

A summary of pharmacokinetic data is presented in Table 1. There were no statistically significant differences between the values of $\text{AUC}_{0-12}$, $C_{\text{max}}$, $T_{\text{max}}$, or $t_{1/2}$ for ddl before and after treatment with clarithromycin. Adverse events that may have been attributable to clarithromycin were minimal in frequency and significance.

The kinetics of ddl found in this study are generally similar to those reported previously [7, 9], although the fact that different doses and formulations were used in previous studies make comparisons difficult. The metabolic fate of ddl in humans is incompletely characterized. Of the quantity of ddl reaching the systemic circulation, 30%–50% appears in the urine as unchanged drug, and the remainder is excreted as various metabolites that appear to be products of xanthine oxidase or other purine metabolic pathways [9]. The bioavailability and $t_{1/2}$ of ddl in dogs receiving this drug under conditions mimicking those in humans are similar to these pharmacokinetic parameters in humans [8]. In addition, in these animals, ddl metabolites via xanthine oxidase appear in plasma and/or urine and consist primarily of allantoin and lesser quantities of uric acid, hypoxanthine, and xanthine. Since the pharmacokinetics of ddl in dogs are similar to those in humans (on the basis of limited studies), similarities in metabolic route between the two species (i.e., via xanthine oxidase) may explain the lack of an interaction found in the trial described herein.

Clarithromycin, like many other macrolides, is an inhibitor of the cytochrome metabolic enzyme P450III-A4 [2]. However, we found that clarithromycin did not have a statistically significant effect on the pharmacokinetics of ddl. This conclusion must be tempered by the observation that there is wide between-subject and within-subject variability in ddl AUCs in this study, and this variability may be obscuring a subtle but real effect of clarithromycin. Alternatively, there may be a subset of subjects in whom a real effect occurs, but the mean effect is negligible.

If a real effect of clarithromycin exists, there is a mechanism that could explain these observations. Instability in the acidic environment of the stomach requires that ddl be administered with buffering agents. Clarithromycin has been shown to increase human gastrointestinal motility at daily doses one-quarter (250 mg b.i.d.) of those used in our study [10]. If clarithromycin accelerates ddl elimination from the stomach (by decreasing gastric emptying time), a decreased acidic degradation of ddl could potentially increase the amount of ddl available for absorption. This may explain why some subjects experienced substantial increases in ddl AUC when ddl was taken with clarithromycin.

Nevertheless, these data argue that the rate of metabolism of ddl is not limited by P450 enzymes inhibited by clarithromycin. We conclude that clarithromycin may be safely given to HIV-infected patients who are receiving ddl.

J. Gregory Gillum, Vivian L. Bruzzese, Debra S. Israel, Lisa G. Kaplowitz, and Ron E. Polk
School of Pharmacy, Department of Pharmacy and Pharmaceutics, and School of Medicine, Division of Infectious Diseases, Medical College of Virginia/Virginia Commonwealth University, Richmond, Virginia

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References

Female Genital Blastomycosis: Case Report and Review

We report a case of female genital blastomycosis that presented as an ovarian tumor and was successfully treated with itraconazole. To our knowledge, this is only the fourth reported case of female genital blastomycosis in the literature.

A 28-year-old female was admitted to the hospital in December 1993 with shortness of breath and increased abdominal girth of 6 weeks' duration. She also complained of weight gain, loss of appetite, and fever (38°C). She had never traveled outside the New Orleans area and was not involved in any outdoor activity. Physical examination was remarkable for a temperature of 38.1°C, decreased breath sounds at both lung bases with dullness to percussion, and massive ascites. Her WBC count was 11,100/mm³ with 71% polymorphonuclear leukocytes, 14% lymphocytes, and 11% monocytes. Analysis of blood chemistry yielded normal results, but a carcinoembryonic antigen, CA125, was elevated (293 IU/mL; normal level, <25). A chest roentgenogram showed bilateral basilar atelectasis with minimal pleural effusion.

Paracentesis was performed, yielding sterile serous fluid with only 4 granulocytes/mm³. A CT scan of the abdomen and pelvis showed a right ovarian lesion. Nodular pleural thickening was noted on a CT scan of the chest. The patient underwent exploratory laparotomy; a 6-cm right tubo-ovarian abscess was discovered, with numerous small nodules along the surface of the peritoneum and the small intestine. A right salpingo-oophorectomy was performed. The only antibiotics administered were prophylactic perioperative doses of a cephalosporin. Histopathologic examination showed a tubo-ovarian abscess, pyogranulomas in the fallopian tube and the peritoneal nodules, and giant cells containing fungal inclusions. A Grocott-Gomori methenamine–silver nitrate stain showed broad-based budding yeast (figure 1). Numerous WBCs, but no organisms, were seen on a gram stain. A KOH smear was negative, but the fungal culture of the tubo-ovarian abscess and peritoneal nodules yielded pure colonies of broad-based budding yeast, which were identified as Blastomyces dermatitidis. Repeated cultures of urine and vaginal secretions were negative for fungi.

The patient's steady sexual contact had no evidence of cutaneous or genitourinary infection; findings on physical examination were normal, and results of a urine culture were negative. Itraconazole monotherapy (200 mg per os, once daily) induced a good clinical response (apyrexia and resolution of the ascites) at 3 weeks and normalization of the abdominal CT scan findings and of the CA125 level at 3 months. There has been no recurrence of infection 1 year after discontinuation of a 6-month therapeutic regimen.

Genitourinary infection is the fourth most common manifestation of blastomycosis after involvement of the lungs, skin, and bones [1, 2]. It has been reported in males almost exclusively as either prostatitis or epididymo-orchitis [1, 3]. Only three cases of female genital blastomycosis can be found in the literature. All the cases presented as tubo-ovarian abscesses; two cases occurred following a distant undiagnosed pulmonary infection [4, 5], and one had been acquired sexually [6]. Peritoneal seeding was present in all three cases.

Our case was different: the patient had no historical or radiographic evidence of antecedent pulmonary infection, and her sexual partner was free of disease; a remote and asymptomatic pulmonary focus was the most likely source of infection. The same assumption has been made to explain an isolated case of splenic abscess caused by B. dermatitidis, which was also complicated by peritoneal seeding [7].

All four of these cases of female genital blastomycosis could have been clinically confused with advanced ovarian cancer with peritoneal involvement. In this context, the marked elevation of the ovarian cancer marker, CA125, is worrisome. Although an elevated CA125 level may in fact be detected in 80% of patients with epithelial ovarian cancers, high values (>500 IU/mL) have been reported for patients with benign conditions, including ascites [8].

Female genital blastomycosis can be acquired through either hematogenous dissemination from an active or dormant pulmonary focus or from sexual contact with a man who has genital blastomycosis. Medical evaluation should include repeated fungal cultures of urine for both the patient and her sexual partner (preferably after prostatic massage). Cultures of vaginal secretions and chest roentgenography are also warranted.

In the absence of meningeal involvement, itraconazole per os (200–400 mg daily) is the recommended therapy for both pulmonary and extrapulmonary blastomycosis. An extended duration of

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* Current affiliation: Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia.

Reprints or correspondence: Dr. Eric L. Mounin, Acute Communicable Diseases Control, Los Angeles County Department of Health, 313 North Figueroa Street, Room 231, Los Angeles, California 90012.

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